PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Heavy-Metal Salts of 2-Mercaptopyridine-1-Oxides and methods of preparing same

We, OLIN MATHIESON CHEMICAL CORPORATION, formerly Mathieson Chemical Corporation, a Corporation organized and existing under the laws of the State of Virginia, United States of America, of 745 Fifth Avenue, New York 22, New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to and has for its object the provision of:—(A) heavy-metal salts (as hereinafter defined) of 2-mercaptopyridine-1-oxides, I, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group; and (B) methods of preparing same. The terms "lower-alkyl" and "lower-alkoxy," as employed herein, mean radicals having from one to seven carbon atoms.

The salts of this invention are active against a wide group of microorganisms, as indicated by the following *in vitro* spectra (data on the antibacterial agent aspergillic acid being included for comparison).

TABLE I

ANTIBACTERIAL ACTIVITY

Salt of 2-mercapto-pyridine-1-oxide	MIC μg/ml.		
	Staph. 209—P	K. Pneum.	BCG
Cupric	—	—	0.06
Zinc	0.6	1	0.02
Manganese	0.15	2.5	0.015
Ferrous	0.25	30	0.015
Ferric	0.12	30	0.01
Mercuric	0.08	0.6	0.012
Silver	0.08	1.5	0.01
Antimonous	0.12	2	0.007
Cobaltous	0.12	12	0.025
Lead	0.12	7	0.06
Bismuth	0.15	1.5	0.01
Aspergillic Acid	20	30	4

TABLE II
ANTIFUNGAL ACTIVITY

	MIC μg/ml											
	Salt of 2-mercaptopyridine-1-oxide											
Microorganism	Control*	Cupric	Zinc	Manganese	Ferrous	Ferric	Mercuric	Silver	Antimonous	Cobaltous	Lead	Bismuth
Aspergillus fumigatus	12.5	3	3	1.6	3.1	1.5	1.6	0.8	0.8	1.6	3.1	0.8
Aspergillus niger	3.1	25	6	1.6	13	3.1	3.1	1.6	0.8	3.1	3.1	1.6
Microsporum canis	—	—	—	3.1	13	6.3	1.6	3.1	1.6	3.1	6.3	3.1
Epidermophyton floccossum	—	—	—	0.8	6.3	1.5	1.6	1.6	0.8	0.8	3.1	0.8
Candida albicans	50	100+	3	3.1	13+	13	6.3	6.3	13	13+	13+	13+
Microsporum audouini	3.1	3	3	0.8	1.6	13	0.8	0.8	0.8	1.6	1.6	0.8
Rhodotorula glutinis	3.1	6	3	1.6	13+	13+	6.3	1.6	1.6	3.1	3.1	1.6
Saccharomyces cerevisiae	1.6	3	3	0.8	3.1	6.3	3.1	1.6	6.3	1.6	13	13
Trichophyton mentagrophytes	3.1	3	3	0.8	3.1	1.5	1.6	0.8	0.8	0.8	1.6	0.8
Fusarium bulbigenum	50	25	3	3.1	13+	13	3.1	3.1	1.6	3.1	6.3	6.3
Ceratostomella ulmi	3.1	3	3	0.8	1.6	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Penicillium notatum	12.5	3	3	1.6	13	6.3	3.1	1.6	0.8	3.1	3.1	1.6

* 8-hydroxyquinoline

Additional *in vitro* tests show that a dosage of 10 ppm. of the iron, zinc, cobalt, lead or bismuth salt of the invention produces 100% inhibition of *Aspergillus niger;* and the manganese, mercuric, silver, or antimony salt is effective in even smaller concentrations. Tests of the aforenamed derivatives of this invention (and of the copper salt) show that total inhibition of *Chaetonium globosum, Myrothecium* B *verrucaria,* and *Aspergillus terreus* results when the derivatives are present in concentrations of 2.5 ppm. or less, 5.0 ppm. or less, and 10 ppm. or less, respectively.

Since the derivatives of this invention possess broad antibacterial and antifungal spectra, they are utilizable in agriculture against plant diseases (for example, against *Peronospora* growing on grapevine), as preservatives (for example, in leather, paper, and prints), and (especially) in plastics and fabrics to render them proof against mildew or other fungus attack. In the protection of fabrics (for example) with the derivatives of this invention, the derivative may be applied to, and/or incorporated in, the fabric in a number of ways. For example, the fabric may be impregnated with the derivative or one of the moieties thereof (as explained hereinafter), *inter alia,* by soaking or spraying. Thus the fabric may be impregnated with a 2-mercaptopyridine-1-oxide (I) or a water-soluble salt thereof, by soaking it in a solution thereof; and the impregnated fabric is then treated with a solution of the salt of the desired heavy-metal and an acid; and the reverse of this procedure can also be used. Preferably, however, the fabric is successively treated with an aqueous solution of an alkali-metal salt of I, and with a water-soluble heavy-metal salt.

The derivatives of the invention are also valuable chemotherapeutic agents, *inter alia,* as fungicides in the treatment of *Dermatophytosis pedis.* For this purpose, a cupric derivative of 2-mercaptopyridine-1-oxide, for example, would be employed with a suitable inert carrier, diluent or base, e.g. starch, talc, magnesium silicate or other carrier to form a dusting powder. When it is desired to employ the derivatives in the form of ointments, the derivative (for example, the zinc derivative of 2-mercaptopyridine-1-oxide) is incorporated in a suitable ointment base (for example, a conventional hydrophilic ointment base).

The salts of this invention may be prepared by a method which comprises interacting a 2-mercaptopyridine-1-oxide (I), preferably a water-soluble salt thereof (e.g. an alkali metal salt such as sodium or potassium salt thereof, or ammonium salt thereof), with a water-soluble salt of an acid and the desired heavy-metal (II) in a solvent for the reactants and recovering the required heavy-metal salt of the reaction product. (When reactant I is a 2-mercaptopyridine-1-oxide *per se* the solvent is preferably alcohol, *cf.* Example 15; and an aqueous solution is used when the 2-mercaptopyridine-1-oxide reactant is in a water-soluble salt form.) An aqueous solution of each reaction may be used. Reactant I may be in tautomeric equilibrium with the corresponding N-hydroxy-2-pyridinethione. This tautomerism will not be alluded to hereinafter, it being understood that such tautomeric form *i.e.* N-hydroxy-2-pyridinethione) is included when referring to the compounds of this invention by a name such as 2-mercaptopyridine-1-oxide.

Examples of the utilizable compounds I include the following (*inter alia*) and water-soluble salts thereof: 2-mercaptopyridine-1-oxide, 3 (4, 5 or 6)-ethoxy-2-mercaptopyridine-1-oxide, 2-mercapto-3 (4, 5, or 6)-methylpyridine-1-oxide, 2-mercapto-3 (4, 5 or 6)-methoxypyridine-1-oxide, 3 (or 5)-bromo-2-mercaptopyridine-1-oxide, 2-mercapto-3 (4, 5 or 6)-ethylpyridine-1-oxide, 3 (or 5)-chloro-2-mercaptopyridine-1-oxide, 3, (4, 5 or 6)-butoxy-2-mercaptopyridine-1-oxide. (See for example, J.A.C.S. 72:4362 for preparation of substituted 2-mercaptopyridine-1-oxides).

The heavy-metal salt reactants (II) utilizable in the practice of this invention include salts in which the heavy-metal group is (*inter alia*) copper, iron, manganese, tin, mercury, cobalt, chromium, arsenic, antimony, lead, gold, cadmium, nickel, silver, bismuth, and zinc (the term heavy-metal, as employed herein and in the appended claims, include the heavy metals and amphoteric metals, such as arsenic, having a specific gravity greater than four. The reactants II may be (*inter alia*) nitrates, acetates, sulphates, and (preferably) halides.

The following examples are illustrative of, but not limitative of, the invention.

EXAMPLE 1

Preparation of the Manganese Salt of 2-mercaptopyridine-1-oxide

A solution of 0.99 g. (0.005 M.) manganese chloride tetrahydrate in 50 cc. of water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. of normal sodium hydroxide. The desired product, a yellow solid, precipitates immediately and is filtered, washed with water, alcohol, and ether, and is air-dried. Weight about 1.3 g.

EXAMPLE 2.

Preparation of the Nickel Salt of 2-mercaptopyridine-1-oxide

A solution of 1.18 g. (0.005 M.) nickel chloride hexahydrate in 50 cc. water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a brown solid, precipitates immediately, and is filtered, washed with water, alcohol, and ether, and is

air-dried. Weight about 1.26 g.

EXAMPLE 3

Preparation of the Ferric Salt of 2-mercaptopyridine-1-oxide

A solution of 1.35 g. (0.0033 M.) of ferric nitrate in 50 cc. water containing approximately 10 cc. 10% HNO_3 is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. of N NaOH. The desired product, a blue solid, precipitates immediately, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 1.33 g.

EXAMPLE 4

Preparation of the Ferrous Salt of 2-mercaptopyridine-1-oxide

A solution of 0.85 g. (0.005 M.) $FeSO_4$ (86%) in 50 cc. water containing 15 cc. 10% H_2SO_4 is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a green solid, precipitates, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 1.15 g.

EXAMPLE 5

Preparation of the Mercuric Salt of 2-mercaptopyridine-1-oxide

A solution of 1.59 g. (0.005 M.) of mercuric acetate in 50 cc. water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a white solid, precipitates, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 2.13 g.

EXAMPLE 6

Preparation of the Mercurous Salt of 2-mercaptopyridine-1-oxide

A solution of 2.8 g. (0.01 M.) $HgNO_3.H_2O$ in 50 cc. water containing approximately 15 cc. 10% HNO_3 is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a grey solid, precipitates, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 2.67 g.

EXAMPLE 7

Preparation of the Silver Salt of 2-mercaptopyridine-1-oxide

A solution of 1.69 g. (0.01 M.) silver nitrate in 50 cc. water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. sodium hydroxide. The desired product, a white solid, forms, and is filtered, washed with water, alcohol and ether and air-dried. Weight about 2.41 g.

EXAMPLE 8

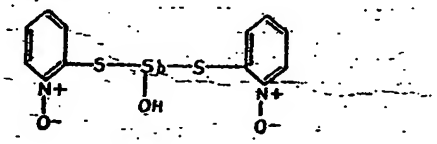
Preparation of the Auric Salt of 2-mercaptopyridine-1-oxide

A solution of 3.03 g. (0.01 M.) auric chloride in 50 cc. water is added to a solution of 3.81 g. (0.03 M.) 2-mercaptopyridine-1-oxide in 30 cc. normal sodium hydroxide. The desired salt which precipitates is filtered, washed with water, alcohol, ether and air-dried.

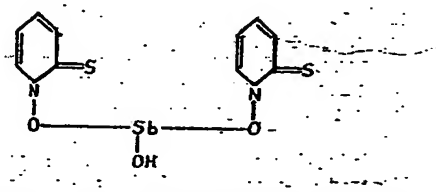
EXAMPLE 9

Preparation of the Antimony Salt of 2-mercaptopyridine-1-oxide

A solution of 0.76 g. (0.0033 M.) of antimony trichloride in 50 cc. water containing approximately 15 cc. 20% HCl is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a white solid, precipitates immediately, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 1.3 g. (It appears from analysis that 2 moles of 2-mercaptopyridine-1-oxide react with one mole of the antimony compound.) The product is believed to have the following formula:



or



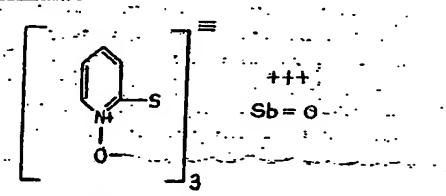
(The bismuth and arsenic salts are believed to have corresponding structure.)

EXAMPLE 10

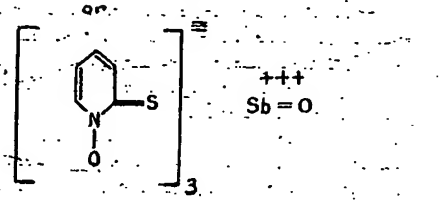
Preparation of the Antimony Salt of 2-mercaptopyridine-1-oxide

A solution of 2.99 g. (0.01 M.) of antimony pentachloride in 100 cc. water containing approximately 50 cc. of 20% HCl is added to a solution of 6.35 g. (0.05 M.) 2-mercaptopyridine-1-oxide in 50 cc. normal sodium hydroxide. The desired salt which precipitates is filtered, washed with water, alcohol, ether and air-dried.

The product is believed to have the following formula:



or



EXAMPLE 11

Preparation of the Cobaltous Salt of 2-mercaptopyridine-1-oxide

A solution of 1.56 g. (0.005 M.) $Co(NO_3)_2.6H_2O$ in 50 cc. water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a gold-coloured solid, precipitates, and is filtered, washed with water, alcohol and ether and air-dried. Weight about 1.35 g.

EXAMPLE 12

Preparation of the Lead Salt of 2-mercaptopyridine-1-oxide

A solution of 1.66 g. (0.005 M.) lead nitrate in 50 cc. water is added to a solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a pale yellow solid, precipitates, and is filtered, washed with water, alcohol and ether and air-dried. Weight about 1.88 g.

EXAMPLE 13

Preparation of the Bismuth Salt of 2-mercaptopyridine-1-oxide

A solution of 1.62 g. (0.0033 M.) $Bi(NO_3)_3.5H_2O$ in 50 cc. water containing 15 cc. 10% HNO_3 is added to a solution of 1.27 g. (0.01 M.). 2-mercaptopyridine-1-oxide in 10 cc. normal sodium hydroxide. The desired product, a light yellow solid, precipitates, and is filtered, washed with water, alcohol, and ether and air-dried. Weight about 1.69 g.

EXAMPLE 14

Preparation of the Arsenic Derivative of 2-mercaptopyridine-1-oxide

A solution of 1.81 g. (0.01 M.) arsenic trichloride in 50 cc. water containing approximately 20 cc. 20% HCl is added to a solution of 3.81 g. (0.03 M.) 2-mercaptopyridine-1-oxide in 30 cc. normal sodium hydroxide. The desired product which precipitates is filtered, washed with water, alcohol, ether and air-dried.

EXAMPLE 15

Preparation of the Cupric Salt of 2-mercaptopyridine-1-oxide

A solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 15 cc. alcohol is added to a solution of 1.25 g. (0.005 M.) $CuSO_4.5H_2O$ in 100 cc. water. The desired product, a dark green precipitate, forms immediately, and is filtered, washed with water, alcohol, and ether. Weight about 1.3 g.

EXAMPLE 16

Preparation of the Zinc Salt of 2-mercaptopyridine-1-oxide

A solution of 1.27 g. (0.01 M.) 2-mercaptopyridine-1-oxide in 15 cc. alcohol is added to a solution of 1.44 g. (0.005 M.) $ZnSO_4.7H_2O$ in 150 cc. water. The desired product, a white precipitate, forms immediately, and is filtered, washed with water, alcohol, and ether and air-dried. It weighs about 1.3 g.

Using molar equivalents of 2-mercapto-6-methylpyridine-1-oxide or 5-bromo-2-mercaptopyridine-1-oxide in place of 2-mercaptopyridine-1-oxide in Example 13, yields the zinc salts of the corresponding 6-methyl and 5-bromo substituted compounds.

EXAMPLE 17

Preparation of the Cadmium Salt of 2-mercaptopyridine-1-oxide

A solution of 1.83 g. (0.01 M.) cadmium chloride in 50 cc. water is added to a solution of 2.54 g. (0.02 M.) 2-mercaptopyridine-1-oxide in 20 cc. normal sodium hydroxide. The desired salt which precipitates is filtered, washed with water, alcohol, ether and air-dried.

What we claim is:—

1. A heavy-metal (as hereinbefore defined) salt of 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined).

2. A method of producing a heavy metal salt as claimed in Claim 1, which comprises interacting 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined) or a water-soluble salt thereof, with a water-soluble salt of an acid and the desired heavy-metal, in a solvent for the reactants, and recovering the heavy metal salt thus formed.

3. A method as claimed in Claim 2, wherein the 2-mercaptopyridine-1-oxide is an alkali-metal salt of a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined).

4. A method of producing a heavy metal salt as claimed in Claim 1, which comprises interacting an aqueous solution of an alkali-metal salt of a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined), with an aqueous solution of a heavy-metal salt of an acid, and recovering the heavy-metal salt thus formed.

5. A fabric impregnated with a heavy-metal (as hereinbefore defined) salt of a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined).

6. The method of treating fabrics which comprises impregnating the fabric with a heavy-metal (as hereinbefore defined) salt of a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined).

7, The method of treating fabrics with a heavy-metal (as hereinbefore defined) salt of a 2-mercaptopyridine-1-oxide, which comprises

impregnating the fabric with a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined), or a water-soluble salt thereof, by soaking the fabric in a solution of the aforesaid oxide, and subsequently treating the fabric with a solution of a water-soluble heavy-metal salt of an acid.

8. The method as claimed in Claim 7, wherein an aqueous solution of an alkali-metal salt of 2-mercaptopyridine-1-oxide and of the water-soluble heavy-metal salt of an acid is used.

9. A fungicidal plant protective preparation comprising an inert diluent and, as a fungicidal agent, a heavy-metal (as hereinbefore defined) salt of a 2-mercaptopyridine-1-oxide, in which the pyridine nucleus may be substituted by a halogen atom or by a lower alkyl or lower alkoxy group (as hereinbefore defined).

10. A method of producing a heavy-metal salt of 2-mercaptopyridine-1-oxide substantially as herein described.

Dated this 19th day of May, 1954.

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